Anemia

Definitions:
➢ Hematocrit <41% in men or <36 in women
➢ Hemoglobin <13.5 gm/dL in men or <12 gm/dL in women

1- Iron deficiency:
- MCC: blood loss (GI, menstrual)
- Presentation: depends on severity (usual presentation of anemia): fatigue, palpitations, SOB, pallor, nail changes (brittle, spoon-shaped), glossitis, pica.
- Moderate – severe anemia -> systolic ejection murmur (“flow” murmur)
- Labs: ↓ Hgb, ↓ MCV, ↓ MCH, ↓ ferritin, ↓ iron, ↓ retics, ↑ TIBC, ↑ RDW
- Tx: most effective is oral therapy w/ ferrous sulfate tablets

2- Anemia of chronic disease:
- Chronic inflammation -> hepcidin -> binds to ferroportin -> traps iron w/ in macrophages + prevents gut iron absorption
- Labs: ↓ Hgb, ↓ MCV, ↓ MCH, ↓ iron, ↓ retics, ↓ TIBC, ↑ ferritin
- Tx: correct underlying cause. If renal ds or chemo/radio-therapy related anemia -> iron supplementation and erythropoietin

3- Sideroblastic anemia:
- Defect in iron metabolism -> iron is trapped in the mitochondria of nucleated RBCs
- Hereditary: defect in aminolevulinic acid synthase or vit B6 metabolism
- Acquired: chloramphenicol, isoniazid, alcohol, lead poisoning
- Can progress into AML
- Labs: ↓ Hgb, ↓ MCV, ↑ ferritin, ↑ iron, ↑ retics, ↓ TIBC
- Specific Dx: Prussian Blue stain of RBCs in BM -> ringed sideroblasts + basophilic stippling
- Tx: best first step: pyridoxine -> response indicates underlying cacuse. Transfusion. BMT.

4- Thalessemia:

Alpha thalessemia:
- 1 genes deleted -> normal pt
- 2 genes deleted -> silent carrier or mild anemia (Hct 30-40%), very low MCV.
- 3 genes deleted -> Hemoglobin H: profound anemia (Hct 20-30%), very very low MCV
- 4 genes deleted -> Hemoglobin Barts: death in utero (hydrops fetalis)
Beta thalassemia:
- **Trait** -> mild anemia + markedly low MCV
- **Major (Cooley anemia)** -> sx start after the age of 6 mo (switch from fetal Hgb to adult Hgb) -> growth failure, hepatosplenomegaly, jaundice, bony deformities (extramedullary hematopoiesis) -> chronic anemia + transfusion dependence -> hemochromatosis, cirrhosis, CHF

- Labs: ↓ Hgb, ↓↓ MCV (disproportionate to the anemia), N ferritin, N iron, N TIBC, N RDW
- **Specific Dx:** Hemoglobin electrophoresis.
  - Beta thalassemia: high levels of Hgb F and A2
  - Alpha thalassemia: normal levels of Hgb F and A2, if 3 genes deleted -> Hgb H
- **Blood smear** -> target cells, poikilocytes
- **Tx:**
  - Trait -> no Tx
  - Beta thalassemia major -> transfusion once\twice a mo
  - Chronic transfusion -> iron overload -> oral deferasirox (or deferoxamine via subQ pump)
  - Splenectomy reduces transfusion requirement (indicated in hypersplenism)
  - BMT
  - Iron supplementation is contraindicated

<table>
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<tr>
<th>Hemoglobin type</th>
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<tr>
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</table>

**MACROCYTIC ANEMIA:**

1- **Vitamin B12 (Cyanocobalamine) deficiency:**
- **MCC:** pernicious anemia -> autoimmune destruction of parietal cells -> ↓ production of intrinsic factor
- **Sx:** peripheral neuropathy, position\vibration\autonomic\motor\cranial nerves abnormalities, psychiatric, bowel\bladder\sexual dysfunx, glossitis, diarrhea, abd pain
- **Labs:** ↓ Hgb, ↑ MCV, ↓ retics, ↓ B12
- **Smear:** hypersegmented neutrophils, RBCs are oval macrocytes (while in hemolysis, liver ds, myelodysplasia give round macrocytes)
- **Specific Dx:** antibodies to IF
- **Tx:** replacement w\vit B12 -> oral daily or parenteral (IM or subQ) monthly (recommended for neuropathy pts)
  - Early in Tx, pts might experience hypokalemia and fluid overload due to ↑ erythropoiesis, cellular uptake of K, and ↑ blood volume

2- **Folic acid deficiency:**
- **Causes:** ↓ dietary intake, pregnancy, skin losses in eczema, ↑ loss from dialysis, phenytoin, alcohol
- Same labs and presentation as vit B12 def, except ↓ folic acid
- **Tx:** oral replacement
HEMOLYTIC ANEMIA:

- Can happen in:
  1) Spleen\liver -> **extravascular**
  2) Vasculature itself -> **intravascular** -> hemoglobinuria
- General Sx: splenomegaly, jaundice, icterus, pruritus, gallstones, hemosiderinuria
- General Labs: normocytic anemia, ↑ LDH, ↓ haptoglobin “hemoglobin eats haptoglobin”, ↑ total bilirubin (indirect specifically), ↑ retics (unlike anemia of chronic ds)
- All hemolytic anemia pt should get folate supplementation!

**A. Coomb’s (-) = Hereditary = Not Immune-related:**

- Sickle cell disease (AR)
- Hereditary spherocytosis (AD)
- Paroxysmal nocturnal hemoglobinuria (PNH) (NOT HEREDITARY!)
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency (XLR)

**B. Coomb’s (+) = Acquired = immune related -> sudden, associated w\ constitutional sx:**

- Warm autoimmune hemolytic anemia
- Cold-agglutinin hemolytic anemia
- Drug-induced hemolytic anemia

**1- Sickle cell disease:**

Pathogenesis:

- Autosomal *recessive*, homozygous: normal Hb A -> **mutant Hb S**
- Point mutation: 6th position of B-chain: valine -> glutamic acid
- Hypoxia, acidosis, temp changes, dehydration, infec -> Hb molecules polymerize -> RBCs sickle -> obstruct vessels -> ischemia

Sickle cell trait:

- Heterozygous, identified by screening (clinically asx) -> genetic counselling
- Not anemic, normal life expectancy
- Associated w\ **isosthenuria** (inability to conc urine)

**Clinical features:**

1. Hemolytic anemia:
   - Jaundice, pallor
   - Pigmented gallstones
   - Leads to high-output CHF
   - Aplastic crisis: provoked by virus (human parvovirus B19) -> treated by blood transfusion (recovers in 7-10 days)

(top to bottom)

CNS: stroke
Eyes: proliferative retinopathy, retinal infarcts
Lungs: infections, ACS
Heart: anemia -> high-output CHF
Blood: chronic hemolytic anemia, aplastic crisis
Kidneys: hematuria, papillary necrosis, renal failure
GI: gallstones, splenic infarctions, abdominal crises
Genitalia: priapism
Bones: painful crises, osteomyelitis, avascular necrosis
2. **Vaso-occlusion:**

- Painful crisis involving bone, multiple sites, self-limiting (2-7 d)

- **Hand-foot syndrome (dactylitis):**
  - Avascular necrosis of metacarpal\metatarsal bones -> painful swelling of dorsa of hands + feet -> in infants\early child (4-6 mo)
  - Often first manifestation of SCD

- **Acute chest syndrome:**
  - Due to repeated episodes of pulmn infarctions
  - Same presentation as pneumonia: chest pain, resp distress, pulmn infiltrates, hypoxia

- **Splenica infarctions (repeated episodes) -> autosplenectomy** (large spleen in childhood -> not palpable by 4 yo; reduced to a small calcified ruminant)

- **Avascular necrosis of joints:** MC hip and shoulder

- **Priapism:**
  - Erection lasting for 30m-3hr due to vaso-occlusion, if lasting > 3hrs -> medical emergency
  - After passing urine, light exercise, cold shower -> usually subsides spont
  - Prevention: hydralazine or nifedipine or using antiandrogen

- **Delayed growth and sexual maturation; esp boys**

- **CVA:** due to cerebral thrombosis, mainly in children

- **Eye complications:** retinal infarcts, vitreous hemorrhage, proliferative retinopathy, retinal detachment

- **Renal papillary necrosis + painless hematuria:** common, may cease spont

- **Chronic leg ulcers:** due to vaso-occlusion, typically: over lateral malleoli

- **Infections:**
  - Functional asplenia -> more susceptible to infections (esp encapsulated bacteria: Hemophilus influenza and Strept pneumonieae)
  - Splenic malfunction -> predisposition to Salmonella osteomyelitis

**Diagnosis:**

- **Labs:** ↓ Hgb, ↑ retics (bc of chronic compensated hemolysis), ↑ LDH, ↑ bilirubin

- **Initial test:** peripheral smear: Sickle-shaped RBCs (negative in sickle cell trait) + Howell-Jolly bodies (precipitated remnants of nuclear material in RBCs of asplenic pts)

- **Most accurate:** Hb electrophoresis

- *The first clue to parvovirus is a sudden drop in reticulocyte level*

**Treatment:**

- Pt education: avoid high altitudes, maintain fluid intake, treat infections promptly

- **Vaccination (S. pneumoniae, H. influenza, Neisseria meningitides)**

- Prophylactic penicillin for children (4 mo – 18 yr)

- Folic acid supplement (bc of chronic hemolysis)
  - Painful crises: hydration, morphine, keep pt warm, supplemental oxygen
  - **Hydroxyurea:** enhances Hb F levels -> interferes w\ sickling, reduces incidence of painful crises, accelerates healing of leg ulcers

- Blood transfusion: based on clinical condition and not Hb levels

- **Exchange transfusion indications** -> ACS, stroke, priapism, visual disturbance from retinal infarction. If exchange transfusion is not available -> give PRBCs
2- Hereditary spherocytosis:
- Autosomal dominant -> loss of spectrin in RBC membrane
- Sx: mild/moderate sx of anemia, splenomegaly, jaundice
- Labs: ↓ Hgb, ↑ MCV, ↑ MCHC, ↑ retics, ↑ LDH, ↑ bilirubin
- Blood smear -> spherocytes :)  
- Negative Coomb’s test
- + Osmotic fragility test -> cells have an ↑ sensitivity to lysis in hypotonic solution
- Tx: folate + elective splenectomy

3- Paroxysmal nocturnal hemoglobinuria (PNH):
- Idiopathic\not hereditary -> clonal defect of GPI in RBC membrane -> ↑ complementation -> intravascular hemolysis
- Why occurs at night? Complementation is encouraged by the slightly acidotic state during sleep
- Sx: anemia sx, dark\cola\tea-colored urine when pt wakes up -> normalizes as the day goes on, increased risk of venous thrombosis (hepatic “Budd-Chiari”, dermal “painful skin nodules”)
- Dx: acidified serum lysis “Ham” test, flow cytometry for CD55\CD59
- Tx: iron + folate, steroids if severe, elective anticoagulation (mandatory if pregnant or thrombo-embolic events have occured)

4- G6PD:
- X-linked recessive (more in boys) -> deficiency in G6PD -> reduction of NADPH (antioxidant)
- Sx: children + acute -> linked to infection, drugs (sulfas, nitrofurantoin), foods (fava beans)
- Blood smear -> Heinz bodies + Bite cells
- Tx: stop offending agent + hydration

5- Autoimmune\warm hemolytic anemia:
- Causes: idiopathic, lymphoproliferative ds (CLL, lymphoma), autoimmune ds (SLE, RA, scleroderma)
- Initial test -> Positive Coomb’s test = direct antiglobulin test (DAT)
- Negative cold-agglutinin titer
- Tx: folate + steroids, transfusion if necessary

6- Cold-agglutinin hemolytic anemia:
- Causes: usually linked to an infection -> Mycoplasma, EBV, HIV
- Key differentiator: worsend w\ exposure to cold -> purplish discoloration of fingers\toes
- Initial test -> Positive Coomb’s test = direct antiglobulin test (DAT)
- Positive cold-agglutinin titer
- Tx: folate + avoid cold conditions, Rituximab if necessary

7- Drug-induced hemolytic anemia:
- MCC: cephalosporin abx, levofloxacin, nitrofurantoin, rifampin, methyldopa
- Initial test -> Positive Coomb’s test = direct antiglobulin test (DAT)
- Tx: stop the drug + folate
**APLASTIC ANEMIA:**

- **Bone marrow failure** -> pancytopenia (anemia, leukopenia, thrombocytopenia)
- **Causes:**
  - Radiation
  - Toxins: benzene
  - Drugs: NSAIDs, chloramphenicol
  - Alcohol
  - Chemo: alkylating agents
  - Infections: hepatitis, HIV, CMV, EBV, parvovirus B19
- **Sx:** bleeding (thrombocytopenia), fatigue (anemia), infections (neutropenia)
- **Dx:** pancytopenia, BM biopsy (**confirmatory**)
- **Tx:** BMT (if young and healthy), immunosuppressive agents (anti-thymocyte globulin, cyclosporine, prednisone)

**Random notes:**

- **Ferritin** and **hepcidin** are acute phase reactants -> elevated in any pt w/ inflammation
- **TIBC** = transferrin
- Hereditary spherocytosis, PNh, G6PD -> are at an increased risk of aplastic anemia (esp w/ parvovirus B19)

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<tr>
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<th>Hgb</th>
<th>MCV</th>
<th>RDW</th>
<th>Retics</th>
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**References:**

- Kaplan step 2 lecture notes
- Paul Bolin’s videos
- Step up to medicine